UNCLASSIFIED

AD 409 834

DEFENSE DOCUMENTATION CENTER

FOR

SCIENTIFIC AND TECHNICAL INFORMATION

CAMERON STATION, ALEXANDRIA, VIRGINIA

UNCLASSIFIED

NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

63 4-2

409824

USNRDL-TR-641
24 April 1963

INHIBITION OF URETHAN LUNG TUMOR INDUCTION IN MICE BY TOTAL-BODY X IRRADIATION

by
W. A. Foley
L. F. Cole

CATALOGED BY DDC
AS AD NO. _____

409 834

DDC
RECEIVED
JUL 12 1963
TISIA B

U.S. NAVAL RADIOLOGICAL DEFENSE LABORATORY

SAN FRANCISCO 24, CALIFORNIA

12ND. P7463

EXPERIMENTAL PATHOLOGY BRANCH
L. J. Cole, Head

BIOLOGICAL AND MEDICAL SCIENCES DIVISION
E. L. Alpen, Head

ADMINISTRATIVE INFORMATION

This work was accomplished under the Bureau of Medicine and Surgery Task MR005.08-1200, Subtask 2, Technical Objective BR 03800, as described in the U. S. Naval Radiological Defense Laboratory Annual Report to the Bureau of Medicine and Surgery (OPNAV FORM 3910-1) of 31 December 1962, and is listed in the U. S. Naval Radiological Defense Laboratory Technical Program Summary for Fiscal Years 1963-1965 of 1 November 1962 under Program A3, Problem 1, entitled "Fundamental Studies in Radiobiology." This study was supported through funds provided by the Bureau of Medicine and Surgery.

AVAILABILITY OF COPIES

Requests for additional copies by agencies or activities of the Department of Defense, their contractors certified to ASTIA, and other government agencies or activities should be directed to the Armed Services Technical Information Agency, Arlington Hall Station, Attn: TIPCR, Arlington 12, Virginia.

Eugene P. Cooper
Eugene P. Cooper
Scientific Director

E. B. Roth, CAPT USN
Commanding Officer and Director

ABSTRACT

Groups of young adult (C57L x A)F_1 mice received a single intraperitoneal injection of urethan prior to or after a single whole body lethal dose of X rays (880 rad) followed by transfusion of normal syngeneic bone marrow to protect against radiation death. This dose of urethan produced multiple tumors in 100% of nonirradiated animals at 24 weeks postinjection. In the irradiated animals there was marked suppression of lung tumor formation, both in number of animals with tumors, and in numbers of tumors per tumor-bearing animal. This suppression was present whether urethan treatment preceded or followed radiation. The results imply that urethan lung carcinogenesis may be interfered with by a direct inhibitory effect of the radiation on cells already altered by urethan, or through latent radiation inhibition of pulmonary alveolar proliferative capacity.

SUMMARY

The Problem:

Administration of the compound, urethan, to certain strains of mice is known to elicit lung tumors in high frequency. Earlier observations showed that mice restored by marrow injection following otherwise lethal doses of X radiation, showed fewer lung tumors than did nonirradiated controls. It was of interest, therefore, to inquire whether similar exposure of mice to high doses of X radiation would suppress the formation of urethan-induced lung tumors.

The Findings:

A single intraperitoneal injection of urethan (1 mg/g body weight) into young adult LAF_1 mice produced multiple lung tumors (mean of 5.6 tumors per mouse) in 100% of the mice sacrificed 24 weeks after injection. When urethan-injected mice received a single whole-body exposure to a lethal dose of X rays (880 rad), followed by isogenic bone marrow transfusion to protect against radiation death, the percentage of mice with pulmonary tumors, and the number of tumors per mouse were sharply reduced. A definite and marked reduction in urethan pulmonary tumor incidence was also observed when the X radiation was given prior to urethan injections. These findings imply that urethan-lung carcino-

genesis may be modified by a direct inhibitory effect of a high dose of X rays on lung cells already altered by urethan, or through latent radiation suppression of alveolar cell proliferative capacity.

INTRODUCTION

The compound, urethan (ethyl carbamate) is a potent carcinogen capable of producing pulmonary tumors in 100% of susceptible animals after a single injection (14, 19). Interest in urethan in our Laboratory followed reports of its effects on bone marrow (18), and experimental evidence of its ability to provide increased radioresistance in mice to X irradiation has been published (6). In the course of these and other experiments the question of radiation sensitivity of urethan tumor induction arose. Observations from several different experiments and certain theoretical considerations, led us to suspect that X irradiation might inhibit urethan pulmonary tumor induction. The experiments reported here show a marked suppression of pulmonary tumor formation when total body X-irradiation (880 rad) was carried out either before or after a single intraperitoneal injection of urethan, which by itself evoked multiple tumors in 100% of nonirradiated control animals.

MATERIALS AND METHODS

Ninety five LAF_1 male mice aged 9-10 weeks (18 - 21 grams) at the time of urethan injection were employed in these experiments. They were housed 7 to 10 per cage in galvanized metal cages with free access to tap water and Purina laboratory chow.

The animals were randomly divided into the following experimental groups: 1) untreated controls; 2) radiation only controls; 3) urethan only controls; 4) urethan followed 1 week later by radiation; 5) urethan

followed 24 hours later by radiation; 6) urethan followed 3 hours later by radiation; 7) radiation followed 3 hours later by urethan.

X irradiation was carried out in a single whole-body exposure of mice in individual, perforated lusteroid tubes on a circular wooden turntable rotating at 3.5 rpm. The dose was 880 rad. The radiation factors were: 250 kvp, 15 ma; filter 0.5 mm Cu plus 1.0 mm Al; HVL, 1.28 mm Cu; 100 cm target to skin distance; dose rate, 30 rad/min. Twenty four hours after this exposure, the irradiated mice received by iv injection approximately 6×10^6 marrow cells from syngeneic (i.e., LAF_1) donors aged 6 - 8 weeks, in order to protect against acute radiation death (5).

All animals were observed until the time of sacrifice, 24 weeks following urethan treatment; and to the same age for the nonurethan controls. They were sacrificed by cervical dislocation, and an immediate gross autopsy done. The extirpated lungs and trachea were fixed intact in Tellyesniczky acetic alcohol formalin (11) for 24 hours. At that time, careful counts of gross pulmonary tumors on the surfaces of the lungs were made, and the tissues were prepared for microscopic examination.

RESULTS

Pulmonary Tumors: The findings on percent of mice with tumors, and number of tumors per mouse are presented in Table I. None of the untreated controls, and only one of the 10 X-ray control mice had a

TABLE I

RADIATION INHIBITION OF
URETHAN PULMONARY TUMOR INDUCTION IN MICE*

TREATMENT	NUMBER OF MICE in group	NUMBER OF MICE with tumors	NUMBER OF TUMORS total	NUMBER OF TUMORS per mouse (mean)**
None	9	0	0	0
X ray only	10	1	1	1
Urethan only	16	16	89	5.6
Urethan, X ray 1 week later	15	8	12	1.5
Urethan, X ray 24 hours later	15	2	2	1.0
Urethan, X ray 3 hrs later	15	2	2	1.0
X ray, Urethan 3 hrs later	15	3	4	1.3

*Male LAF_1, treated at 9 - 10 weeks of age, sacrificed 24 weeks later.

**in tumor-bearing mice.

†X ray - 880 rad whole body X irradiation followed 24 hrs later by 6×10^6 syngeneic marrow cells i.v.

Urethan - ethyl carbamate (U.S.P.) 1 mg/g body weight

pulmonary tumor at the time of sacrifice. Treatment with urethan alone produced multiple tumors (mean of 5.6 per mouse) in 100% of the animals. By contrast, exposure of the urethan-treated mice to 880 rad of X rays sharply reduced the number of mice with pulmonary tumors, when the radiation was administered either 24 hours after, 3 hours after, or 3 hours before the single injection of urethan, i.e., as few as 2 mice with tumors out of 15, versus 16 mice with tumors out of 16. Furthermore, the total number of pulmonary tumors observed was markedly decreased from 89 in the urethan only group to 2 in the groups of mice which received urethan plus radiation 3 hours later or 24 hours later. When the radiation treatment followed urethan by one week, the number of tumor-bearing animals was about half that of the control, urethan only, group, and the average number of tumors per tumor bearing mouse was also reduced (1.5 versus 5.6 tumors per mouse). It is of interest that a definite and marked reduction in urethan pulmonary tumor incidence was also observed when the X radiation was given 3 hours prior to urethan.

Histopathology

All gross pulmonary tumors were confirmed by microscopic examination (Figure 1). They were similar in description to that given by others for spontaneous and urethan-induced neoplasms in the mouse lung (4,20). Both compact and adenoid patterns were observed, sometimes in the same gross lesion, and no difference in histology of the pulmonary tumors could be detected between the irradiated and nonirradiated tumor-bearing

animals. Although no evidence of metastasis was found in these experiments, we have seen extension of such tumors to regional lymph nodes in other experiments in which urethan-treated mice were allowed to live for periods of one year or more after treatment. In addition, seven animals from the present series showed focal areas of "adenomatous" change (Figures 2 and 3) which was morphologically distinct from the tumors, in that they were flush or retracted from the lung surface (in contrast to the bulging of tumors), and on microscopic examination showed areas of alveolar cell proliferation, inflammatory cellular infiltrate, fibrous thickening of alveolar walls, and cellular debris in the alveolar lumina. Two of these mice were in the urethan only group, two in the group given radiation 3 hours after urethan, and one each in the irradiated controls, untreated controls, and in the mice irradiated 24 hours after urethan.

No significant degree of glomerulosclerosis was observed in any of the animals. No cases of leukemia were seen in any of the groups, although microscopic examination of marrow and lymphoid organs was made in all cases. The liver showed no pathology on microscopic examination.

Body Weights

Data on body weights of the animals at the time of sacrifice are given in Table II. Significant differences ($p<0.05$ by Student "t" test) in average body weight at time of sacrifice were observed between each group treated with the combination of urethan and radiation

Fig. 1 Pulmonary alveolar tumors in urethan treated mouse. Adenoid pattern in tumor on right and compact pattern in tumor on left. Note bulging of pleural surface in latter. H & E, 60X.

Fig. 2 An "adenomatous" lesion from a mouse radiated one week after urethan treatment. H & E, 125X.

Fig. 3 Higher magnification of Figure 2. Note proliferation of alveolar cells, and inflammatory reaction. H & E, 250X.

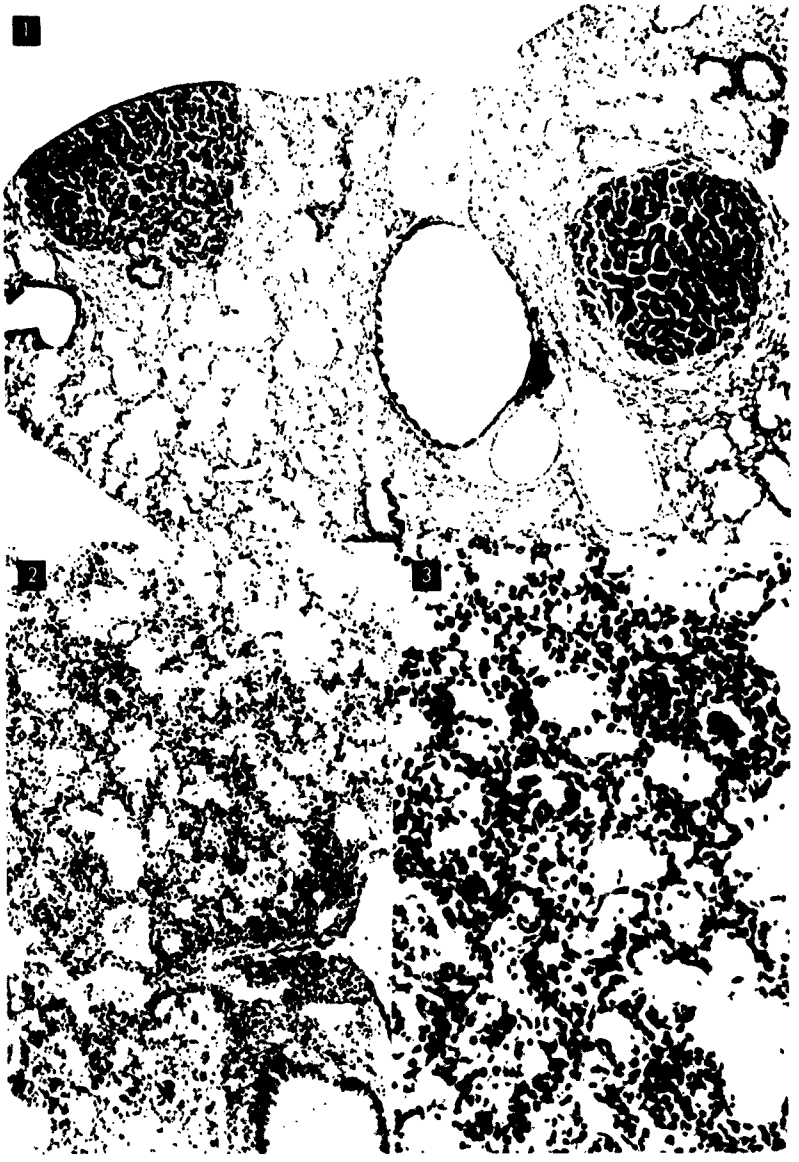
1
2
3

TABLE II

BODY WEIGHT OF URETHAN TREATED AND X-IRRADIATED MICE AT TIME OF SACRIFICE*

TREATMENT	BODY WEIGHT(g)		% MICE WITH TUMORS
	Mean ± S.E.	Range	
None	33.0 ± 0.6	30.3 - 37.5	0
X ray only	29.8 ± 0.8	26.0 - 34.9	10
Urethan only	34.0 ± 0.9	31.4 - 42.5	100
Urethan, X ray 1 week later	27.9 ± 0.5	24.8 - 41.0	53
Urethan, X ray 1 day later	27.5 ± 0.4	25.1 - 30.1	13
Urethan, X ray 3 hrs later	27.2 ± 0.4	24.9 - 30.8	13
X ray, Urethan 3 hrs later	28.1 ± 0.5	24.1 - 31.2	20

*All mice weighed between 18 and 21 grams at time of random selection into groups for treatment. No significant differences in body weight were found between tumor bearing and non-tumor bearing mice in the individual groups.

versus each of the control groups (untreated, urethan only, radiation only), except that the group irradiated before urethan treatment did not differ from the radiation control group. The radiation control group also differed significantly from the untreated and from the urethan only groups.

DISCUSSION

A decreased incidence of pulmonary tumors in mice following large single doses of fast neutrons or X rays has previously been reported from this Laboratory (15) and by others (23) following gamma or neutron radiation. A similar reduction in nitrogen mustard-induced pulmonary tumors after X irradiation has been reported by Heston, et al. (8). The present data support the above findings of a radiation inhibition of alveolar cell proliferation, in this case induced by urethan. They also provide evidence for a latent radiation effect to the alveolar cells, in that mice treated with urethan 3 hours after X irradiation showed decrease in tumor incidence similar to that seen in those treated with urethan before X irradiation. This "latent" radiation inhibition is probably analogous to that previously reported from this Laboratory with respect to proliferative capacity of kidney (7), another tissue whose normal cell turnover rate, like lung, is relatively low. Furthermore, we have not found any histologic evidence of either urethan or X-ray effects on mouse lung in routine preparations studied over an acute (2 week) period following treatment. This observation confirms

previous reports in radiation (16) and urethan (13) experiments, and emphasizes the subcellular site of action of these agents. Urethan is presumed to exert its biological effect through interference with DNA synthesis, possibly at the level of the pyrimidine nucleotides (17). It is also known to be rapidly excreted from the animal body (2,3).

It is probable, on the basis of the above considerations, that this inhibitory effect of X radiation on urethan lung-tumorigenesis is critically dependent on the high radiation dose used. Therefore, at some lower dose level, or with fractionated X radiation (12) the lung carcinogenic effect of radiation may turn out to be additive with that of urethan. Experiments designed to resolve this point are in progress.

The "adenomatous" change seen in a few mice in several of the treatment and control groups is similar to that described by Horn, et al. (9). This lesion bears a microscopical resemblance to the contagious alveolar proliferation (jaagsiekte) in sheep. Similar lesions have been described in man (1). A recent report (22) on such lesions in DBA mice following urethan treatment, interpreted them as a neoplastic response. The specific etiology of this lesion is not known, and the multiplicity of names that have been applied to it bears witness to the lack of agreement which surrounds it. Its occurrence in this study was too infrequent and sporadic to allow any definite conclusions, but we feel with Horn, et al. (9) that this "adenomatous" change is an inflammatory response, and not a true neoplasm.

The mechanism by which a single, high dose of whole body X radiation antagonizes the lung-carcinogenic effect of urethan is not known. At first sight this effect seems perhaps paradoxical, since urethan is itself radiomimetic. We have considered two possible hypotheses: 1) that the radiation produces intracellular damage such that the capacity for proliferation on the part of the alveolar cells is inhibited (at least for a time), and therefore that the population of cells able to emerge as tumors due to the carcinogenic or co-carcinogenic effect of urethan is greatly reduced; 2) that the interaction of urethan with a biochemical "target" (possibly DNA) involved in the carcinogenic change, is somehow interfered with under conditions in which X radiation is applied shortly before (3 hours) or shortly after (3 or 24 hours) urethan. Perhaps there is competition between X radiation and urethan for the same 'target' site. It is noteworthy to point out in support of this concept that the suppressive effect of X radiation on urethan lung-tumorigenesis was appreciably lessened when the radiation was given 1 week after urethan, as compared with 1 day or 3 hours after urethan (Table I). Apparently some urethan-induced changes, related to eventual carcinogenesis, already had occurred in the lung cells within one week after urethan injection.

There remains the possibility that the time of sacrifice in these experiments (24 weeks posttreatment) does not measure the true carcinogenicity of urethan plus radiation; if these animals were allowed to live for a larger fraction of their life span, more tumors might arise

in the irradiated animals. However, it is probable that more tumors per animal also would be found in the animals treated with urethane only (19).

The question of body weight reduction, reflecting reduced caloric intake or urethan toxicity, as a possible factor in suppression of tumor formation must be considered in light of the body weight data (cf 21). The fact that a similar weight reduction failed to give similar tumor inhibition (i.e., in the group irradiated one week after urethan versus the other group), would seem to indicate that failure to gain weight was a concomitant and not a causal factor in pulmonary tumor inhibition. Furthermore, in the experiments of Larsen and Heston (10) decrements in body weight, similar to those observed here, were produced by caloric restriction, but did not elicit significant changes in spontaneous tumor incidence in male strain A mice; still more profound reduction in body weight (by caloric restriction) yielded a smaller reduction in spontaneous pulmonary tumor incidence than was seen in the present experiments.

Experiments are now in progress in the attempt to resolve some of the questions raised by the present findings, i.e., to determine the effect of fractionated X-radiation on urethan-induced lung tumorigenesis; to ascertain whether the radiation effect is direct or indirect through partial shielding; and to evaluate the role of proliferative capacity of alveolar cells, by means of autoradiography.

REFERENCES

1. Bell, E. T. Alveolar Epithelium in Pulmonary Diseases. Am. J. Path., 19: 901-912, 1943.
2. Berenblum, I., Haran-Ghera, N., Winnick, R., and Winnick, T. Distribution of C-14 Labeled Urethans in Tissues of the Mouse and Subcellular Localizations in Lung and Liver. Cancer Research 18: 181-185, 1958.
3. Boyland, E., and Rhodes, E. The Distribution of Urethane in Animal Tissues, As Determined by a Micro Diffusion Method, and the Effect of Urethane Treatment on Enzymes. Biochem. J., 44: 528-531, 1949.
4. Cloudman, M. Spontaneous Neoplasms in Mice. G. D. Snell (ed.), Biology of the Laboratory Mouse, pp 208-212. Philadelphia: The Blakiston Company, 1941.
5. Cole, L. J. Biological Protection Against Radiation Through Bone Marrow Transplantation. B. Rajewsky (ed.), Ninth International Congress of Radiology (Transactions), pp. 156-162. Stuttgart: Georg Thieme Verlag, 1960.
6. Cole, L. J. and Gospe, S. Increased Radioresistance in Mice Injected With Urethane One Day Before X irradiation. Radiation Research, 15: 684-693, 1961.

7. Cole, L. J. and Rosen, V. J. Latent Radiation Inhibition and Recovery of Mitotic Activity in Mouse Kidney. Exper. Cell Research, 23: 416-418, 1961.

8. Heston, W. E., Lorenz, E., and Desinger, M. K. Occurrence of Pulmonary Tumors in Strain A Mice Following Total Body X radiation and Injection of Nitrogen Mustard. Cancer Research, 13: 573-577, 1953.

9. Horn, H. A., Congdon, C. C. Eschenbrenner, A. B., Andervont, H. B., and Stewart, H. L. Pulmonary Adenomatosis in Mice. J. Nat. Cancer Inst., 12: 1297-1315, 1962.

10. Larsen, C. D., and Heston, W. E. Effects of Cystine and Coloric Restriction on the Incidence of Spontaneous Pulmonary Tumors in Strain A Mice. J. Nat. Cancer Inst., 6: 31-40, 1945.

11. Lillie, R. D. Histopathologic Technic and Practical Histochemistry, p 35. New York: The Blakiston Company, 1954.

12. Lorenz, E. Some Biological Effects of Long Continued Irradiation. Am. J. Roentgenology, 63: 176-185, 1950.

13. Mostofi, F. K., and Larsen, C. D. The Histopathogenesis of Pulmonary Tumors Induced in Strain A Mice by Urethane. J. Nat. Cancer Inst., 11: 1187-1221, 1951.

14. Nettleship, A., Henshaw, P. S., and Meyer, H. L. Induction of Pulmonary Tumors in Mice with Ethyl Carbomate (Urethane). J. Nat. Cancer Inst., 4: 309-319, 1943.

15. Nowell, P. C., and Cole, L. J. Late Effects of Fast Neutrons Versus X rays in Mice: Nephrosclerosis, Tumors, Longevity. Radiation Research 11: 545-556, 1959.

16. Rhoades, R. P. The Lung. in W. Bloom (ed.), Histopathology of Irradiation From External and Internal Sources, pp 704-709, New York: McGraw-Hill Book Company, Inc., 1948.

17. Rogers, S. Studies of the Mechanism of Action of Urethan in Initiating Pulmonary Adenomas in Mice II. Its Relation to Nucleic Acid Synthesis. J. Exper. Med., 105: 279-306, 1957.

18. Rosin, A., and Goldhaber, G. Effect of Repeated Doses of Urethane (Ethyl Carbonate) on the Mitotic Activity and Cellular Composition of the Bone Marrow. Blood, 11: 1032-1040, 1956.

19. Shimkin, M. B. Pulmonary Tumors in Experimental Animals. J. P. Greenstein and A. Haddow (eds.), Advances in Cancer Research, 31: 223-267. New York: Academic Press Inc, 1955.

20. Stewart, H. L. Pulmonary Tumors in Mice. F. Homburger and W. H. Fishman (eds.), The Physiopathology of Cancer 1st edition, pp 93-112. New York; Paul B. Hoeber Inc., 1953.

21. Tannenbaum, A. Nutrition and Cancer. F. Homburger and W. H. Fishman (eds.). The Physiopathology of Cancer, 1st ed., pp 392-440. New York: Pau. B. Hoeber, Inc., 1953.

22. Tannenbaum, A., and Maltoni, C. Neoplastic Response of Various Tissues to the Administration of Urethan. Cancer Research, 22: 1105-1112, 1962.

23. Upton, A. C., Kimball, A. W., Furth, J., Christenberry, K. W. and Benedict, W. H. Some Delayed Effects of Atom-Bomb Radiations in Mice. Cancer Research. 20: 1-62, 1960.

INITIAL DISTRIBUTION

Copies

NAVY

3	Chief, Bureau of Ships (Code 210L)
1	Chief, Bureau of Ships (Code 320)
2	Chief, Bureau of Medicine and Surgery
1	Chief of Naval Operations (Op-07T)
1	Chief of Naval Research (Code 104)
3	Director, Naval Research Laboratory (Code 2021)
1	Office of Naval Research (Code 422)
1	Office of Naval Research (Code 441)
10	Office of Naval Research FPO, New York
3	Naval Medical Research Institute
1	OiC, Radiation Exposure Evaluation Laboratory
1	Director, Aviation Medical Acceleration Laboratory
1	U. S. Naval Postgraduate School, Monterey
1	Commander, Naval Ordnance Laboratory, Silver Spring
1	Naval Missile Center (Code 5700)
1	CO, Naval Medical Research Unit No. 2
1	U. S. Naval Hospital, San Diego
1	CO, Naval Medical Field Research Laboratory, Camp Lejeune

ARMY

1	Chief of Research and Development (Atomic Division)
1	Chief of Research and Development (Life Science Division)
1	Deputy Chief of Staff for Military Operations (CBR)
1	Chief of Engineers (ENGMC-DE)
1	Chief of Engineers (ENGCW)
1	CG, Army Materiel Command (AMCRD-DE-NE)
1	U. S. Army Edgewood Arsenal
1	CG, CBR Combat Developments Agency
3	CO, BW Laboratories
1	CO, Fort McClellan, Alabama
1	Commandant, Chemical Corps Schools (Library)
1	CO, Chemical Research and Development Laboratories
1	Commander, Chemical Corps Nuclear Defense Laboratory
1	Hq., Army Environmental Hygiene Agency
1	CG, Aberdeen Proving Ground

1	CO, Army Medical Research Laboratory
1	Army Medical Research and Nutrition Laboratory (MEDEN-AD)
1	CO, Army Medical Service Combat Development Agency
2	Medical Field Service School, Fort Sam Houston (Stimson Lib.)
1	Brooke Army Medical Center (Dept. Prev. Med.)
1	Director, Surgical Research Unit, Fort Sam Houston
1	Director, Walter Reed Army Medical Center
1	Hq., Army Nuclear Medicine Research Detach., Europe
1	CG, Combat Developments Command (CDCMR-V)
1	CG, Quartermaster Res. and Eng. Command
1	Hq., Dugway Proving Ground
3	The Surgeon General (MEDNE)
1	Office of the Surgeon General (Combat Dev.)
1	CO, Engineer Res. and Dev. Laboratory
1	Director, USACDC Nuclear Group
1	CG, Munitions Command
1	CG, Frankford Arsenal
1	CG, Army Missile Command

AIR FORCE

1	Assistant Chief of Staff, Intelligence (AFCIN-3B)
6	CG, Aeronautical Systems Division (ASAPRD-NS)
1	CO, Radiological Health Laboratory Division
1	Director, USAF Project RAND
1	Commandant, School of Aerospace Medicine, Brooks AFB
1	CO, School of Aviation Medicine, Gunter AFB
1	Air Force Special Weapons Center - SWRBB
1	Radiobiological Laboratory
1	Office of the Surgeon (SUP3.1), Strategic Air Command
1	Office of the Surgeon General
1	Commander, Special Weapons Center, Kirtland AFB
1	Director, Air University Library, Maxwell AFB
2	Commander, Technical Training Wing, 3415th TTG
1	Hq., Second Air Force, Barksdale AFB
1	Commander, Electronic Systems Division (CRZT)

OTHER DOD ACTIVITIES

3	Chief, Defense Atomic Support Agency (Library)
1	Commander, FC/DASA, Sandia Base (FCDV)
1	Commander, FC/DASA, Sandia Base (FCTG5, Library)
1	Commander, FC/DASA, Sandia Base (FCWT)
2	Office of Civil Defense, Washington
2	Civil Defense Unit, Army Library
1	Armed Forces Institute of Pathology

20	Commander, Defense Documentation Center
1	Director, Armed Forces Radiobiology Research Institute

AEC ACTIVITIES AND OTHERS

1	Research Analysis Corporation
1	Director, Division of Biology and Medicine
1	NASA, Ames Research Center, Moffet Field
1	Aerojet General, Azusa
5	Argonne Cancer Research Hospital
10	Argonne National Laboratory
2	Atomic Bomb Casualty Commission
1	AEC Scientific Representative, France
1	AEC Scientific Representative, Japan
3	Atomic Energy Commission, Washington
2	Atomic Energy of Canada, Limited
3	Atomics International
2	Battelle Memorial Institute
1	Borden Chemical Company
3	Brookhaven National Laboratory
1	Chicago Patent Group
1	Colorado State University
1	Columbia University (Rossi)
1	Committee on the Effects of Atomic Radiation
3	Defence Research Member
2	duPont Company, Aiken
1	duPont Company, Wilmington
1	Edgerton, Germeshausen and Grier, Inc., Goleta
1	Edgerton, Germeshausen and Grier, Inc., Las Vegas
2	General Dynamics, Fort Worth
2	General Electric Company, Cincinnati
8	General Electric Company, Richland
1	General Electric Company, St. Petersburg
1	General Scientific Corporation
1	Hughes Aircraft Company, Culver City
1	Iowa State University
1	Journal of Nuclear Medicine
1	Knolls Atomic Power Laboratory
2	Los Alamos Scientific Laboratory (Library)
1	Lovelace Foundation
1	Martin-Marietta Corporation
1	Massachusetts Institute of Technology
1	Mound Laboratory
2	NASA, Scientific and Technical Information Facility
1	National Academy of Sciences
1	National Bureau of Standards (Taylor)

1	National Cancer Institute
1	National Lead Company of Ohio
1	National Library of Medicine
1	New Jersey State Department of Health
1	New York Operations Office
1	New York University (Eisenbud)
1	Office of Assistant General Counsel for Patents
2	Phillips Petroleum Company
4	Pratt and Whitney Aircraft Division
2	Public Health Service, Washington
1	Public Health Service, Las Vegas
1	Public Health Service, Montgomery
1	Reynolds Electrical and Engineering Company, Inc.
1	Sandia Corporation, Albuquerque
1	Union Carbide Nuclear Company (ORGDP)
5	Union Carbide Nuclear Company (ORNL)
1	Union Carbide Nuclear Company (Paducah Plant)
1	United Nuclear Corporation (NDA)
1	U. S. Geological Survey, Denver
1	U. S. Geological Survey, Menlo Park
1	U. S. Geological Survey, Naval Gun Factory
1	U. S. Geological Survey, Washington
1	U. S. Weather Bureau, Washington
1	University of California, Davis
3	University of California Lawrence Radiation Lab., Berkeley
2	University of California Lawrence Radiation Lab., Livermore
1	University of California, Los Angeles
1	University of California, San Francisco
1	University of Chicago Radiation Laboratory
1	University of Hawaii
1	University of Puerto Rico
1	University of Rochester (Atomic Energy Project)
1	University of Tennessee (UTA)
1	University of Utah
1	University of Washington (Donaldson)
1	Wayne State University
1	Westinghouse Electric Corporation (NASA)
1	Westinghouse Electric Corporation (Rahilly)
1	Western Reserve University (Friedell)
25	Technical Information Extension, Oak Ridge

USNRDL

41	USNRDL, Technical Information Division

DISTRIBUTION DATE: 12 June 1963

Naval Radiological Defense Laboratory
USNRDL-TR-641
INHIBITION OF URETHAN LUNG TUMOR INDUCTION IN MICE BY TOTAL-BODY X IRRADIATION
by W. A. Foley and L. J. Cole 24 April 1963
24 p. tables illus. 23 refs. UNCLASSIFIED

Groups of young adult (C57L x A)F_1 mice received a single intraperitoneal injection of urethan prior to or after a single whole body lethal dose of X rays (880 rad) followed by transfusion of normal syngeneic bone marrow (over)

1. Urethan.
2. Lungs.
3. Neoplasms.
4. X radiation.
5. Radiation effects.

I. Foley, W. A.
II. Cole, L. J.
III. Title.
IV. MR005.08-1200

UNCLASSIFIED

Naval Radiological Defense Laboratory
USNRDL-TR-641
INHIBITION OF URETHAN LUNG TUMOR INDUCTION IN MICE BY TOTAL-BODY X IRRADIATION
by W. A. Foley and L. J. Cole 24 April 1963
24 p. tables illus. 23 refs. UNCLASSIFIED

Groups of young adult (C57L x A)F_1 mice received a single intraperitoneal injection of urethan prior to or after a single whole body lethal dose of X rays (880 rad) followed by transfusion of normal syngeneic bone marrow (over)

1. Urethan.
2. Lungs.
3. Neoplasms.
4. X radiation.
5. Radiation effects.

I. Foley, W. A.
II. Cole, L. J.
III. Title.
IV. MR005.08-1200

UNCLASSIFIED

to protect against radiation death. This dose of urethan produced multiple tumors in 100% of nonirradiated animals at 24 weeks postinjection. In the irradiated animals there was marked suppression of lung tumor formation, both in number of animals with tumors, and in numbers of tumors per tumor-bearing animal. This suppression was present whether urethan treatment preceded or followed radiation. The results imply that urethan lung carcinogenesis may be interfered with by a direct inhibitory effect of the radiation on cells already altered by urethan, or through latent radiation inhibition of pulmonary alveolar proliferative capacity.

UNCLASSIFIED

to protect against radiation death. This dose of urethan produced multiple tumors in 100% of nonirradiated animals at 24 weeks postinjection. In the irradiated animals there was marked suppression of lung tumor formation, both in number of animals with tumors, and in numbers of tumors per tumor-bearing animal. This suppression was present whether urethan treatment preceded or followed radiation. The results imply that urethan lung carcinogenesis may be interfered with by a direct inhibitory effect of the radiation on cells already altered by urethan, or through latent radiation inhibition of pulmonary alveolar proliferative capacity.

UNCLASSIFIED